Attorney's Docket No. 032904-001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	**MAIL STOP AMENDMENT**
Einar STEFANSSON	Group Art Unit: 1614
Application No.: 09/925,659	Examiner: Zoreh A. Fay
Filed: August 10, 2001	Confirmation No.: 4462
For: METHOD FOR THE PREVENTION AND TREATMENT OF RETINOPATHY	

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, EINAR STEFANSSON, M.D., Ph.D., hereby state as follows:

1. I am a citizen of Iceland, residing at Fjardaras 13, 110 Reykjavik, Iceland.

2. I am attaching the details of my primary academic appointment, medical licensure, specialty certifications and education.

3. My educational degrees include an M.D. from the University of Iceland in 1978 and a Ph.D. from Duke University in physiology in 1981.

4. After interning at the National Hospital of Iceland, I was a Research Associate in Ophthalmology at Duke University Medical Center in 1981.

5. I was a Resident in Ophthalmology at Duke University from January 1, 1982 to December 31, 1984, and since that time have been active in the field of ophthalmology.

6. I was visting scientist at the National Eye Institute, National Institutes of Health 1985 – 1986.

7. I was Assistant Professor in Ophthalmology the the Duke University Medical Center 1987 – 1989.

8. From January 1, 1988 to the present, I have been Professor of Ophthalmology and Academic chairman of the Department of Ophthalmology, University of Iceland.

9. I was Vice Dean of the Medical School of the University of Iceland 1992 - 1996 and Dean of the Medical School 1996 – 1998.

10. Since January 1, 2005, I have served as Chief Editor for *Acta Ophthalmologica Scandinavica*.

11. I am the inventor of the invention described and claimed in the present application.

12. I am familiar with the prosecution history of this application, and the references cited, including the Official Action/Final Rejection mailed December 21, 2004, the references relied upon by the Examiner, and the fact that Claims 6, 12-26, 31 and 37-51, all of the claims in the application, have been rejected.

13. I am setting forth below what I know and/or believe to be true regarding the issues raised by the Examiner:

On page 2 of the Official Action, the Examiner states that claims 6,12-26,31 and 37-51 are rejected under 35 U.S.C. 112, first paragraph, because "the specification, while being enabling for certain carbonic anhydrase inhibitors for slowing the progression of diabetic retinopathy, does not reasonably provide enablement for all carbonic anhydrase inhibitors being used for slowing the progression of diabetic retinopathy in a diabetic not suffering from diabetic retinopathy. "

The systemic sulfonamide drugs that have been used clinically as antiglaucoma agents such as acetazolamide, metazolamide, ethoxyzolamide, dechlorophenamide, dorzolamide, and brinzolamide have in common a basic molecular structure (see *Supuran et al, Carbonic anhydrase inhibitors, Medicinal Research Reviews 23, 146-189, 2003,* see enclosed copy, page 153). These drug molecules inhibit carbonic anhydrase through the same basic molecular

structure. Small differences in other parts of the molecules determine pharmacokinetic properties, such as affinity, water solubility and other physical characteristics. The key issue is that the basic molecular structure and the basic function (carbonic anhydrase inhibition) of all these molecules is the same. See also paragraphs [0022] through [0024] of the present application, especially paragraph [0024].

In studies conducted by myself and co-workers of the physiological functions of these molecules, in particular their effect on oxygenation of the retina and optic nerve and vessel diameters, we have tested acetazolamide, dorzolamide, ethoxyzolamide and methoxyzolamide and found their pharmacological functions as they relate to vasodilatation and increased oxygen tension to be the same with slight differences in their potency (*Stefansson E, Pedersen DB, Jensen PK, la Cour M, Kiilgaard JF, Bang K, Eysteinsson T., Optic nerve oxygenation; Prog Retin Eye Res. 2005 May;24(3):307-32.; Bach Pedersen D, Koch Jensen P, la Cour M, Kiilgaard JF, Eysteinsson T, Bang K, Wiencke AK, Stefansson E, Carbonic anhydrase inhibition increases retinal oxygen tension and dilates retinal vessels. Graefes Arch Clin Exp Ophthalmol. 2005 Feb;243(2):163-8 and Stefansson E, Jensen PK, Eysteinsson T, Bang K, Kiilgaard JF, Dollerup J, Scherfig E, la Cour M. , Optic nerve oxygen tension in pigs and the effect of carbonic anhydrase inhibitors, Invest Ophthalmol Vis Sci. 1999 Oct;40(11):2756-61.)* Copies of these references are enclosed.

The rationale for the effect of the carbonic anhydrase inhibitors is based on their carbonic anhydrase inhibition and in particular their effect on retinal vessel diameter and oxygenation, which we have found to be essentially the same for the various carbonic anhydrase inhibitors mentioned above. It is therefore quite reasonable to expect the clinical effect of all of them to be

in line with the pharmacological effect and therefore expect all of them to be useful in preventing the progression to diabetic retinopathy as we have shown dorzolamide to be in the clinical study described in the present application.

On page 3 of the Official Action, the Examiner states: "The prior art does not recognize that all carbonic anhydrase inhibitors have the same function. Applicant on page 5 of the specification admits that not all carbonic anhydrase inhibitors have the same therapeutic activity. Applicant admits that some of carbonic anhydrase inhibitors have been used as diuretics for treatment of congestive heart failure or in the treatment of allergies". This statement includes a misunderstanding: The class of molecules called carbonic anhydrase inhibitors are indeed classified as such because they have the same function. This common function is the inhibition of the enzyme carbonic anhydrase, including its various isoenzymes. A molecule that does not have this function would not be classified as a carbonic anhydrase inhibitor. What is true, however, is that various molecules in this class of drug molecules differ in their affinity for the carbonic anhydrase isoenzymes, and some of their physical properties such as water solubility etc.

The enzyme carbonic anhydrase is ubiquitous in the body and therefore carbonic anhydrase inhibitors can be used for a number of disease conditions such as glaucoma in the eye, and for diuresis in the kidney. In both cases, the mechanism of action is through the inhibition of carbonic anhydrase. For example, when acetazolamide is used (rarely) as a diuretic it will also influence the intraocular pressure, and when it is used as a glaucoma drug it will also induce some diuresis as a side effect. The desired therapeutic activity may differ with the other therapeutic activities listed as side effects in each case but the actual pharmacologic activity of

the drug would be the same. One exception to this, however, is when carbonic anhydrase inhibitors as applied topically to the eye where the majority of the absorption and therapeutic effect will take place in the eye and there will be only a small effect on kidneys and other parts of the body.

Statement 4 on page 3 in the Official Action is not true. The predictability of the pharmaceutical and chemical art is high in the field of carbonic anhydrase inhibitors. The essential structure of sulfonamide carbonic anhydrase inhibitors is well known and well characterized. The difference between the different molecules in the class only affects the pharmacokinetic properties and distribution and not the basic pharmacological action. (see Supuran et al, Carbonic anhydrase inhibitors, Medicinal Research Reviews 23, 146-189, 2003)

Under paragraph 6 on page 3 in the Official Action, the Examiner states as a general rule: "It is well settled that in cases involving chemical and chemical compounds which differ radically in their properties it must appear in an applicant's specification either by enumeration.....". It is absolutely not true that the different chemical compounds in the class of carbonic anhydrase inhibitors differ radically. All these molecules have the same basic structure which is responsible for the carbonic anhydrase inhibition, which is their common function, and they differ only in moieties which are responsible for differences in pharmacokinetic properties and distribution in the eye and body.(see Supuran et al, Carbonic anhydrase inhibitors, Medicinal Research Reviews 23, 146-189, 2003.)

The general rule by Dreshfield therefore does not apply here since it is unreasonable to state that these particular chemical compounds differ radically in their properties. Note also that in paragraph [0024] of the specification, the carbonic anhydrase inhibitors have been structurally

described as heterocyclic or aryl sulfonamides and the generic and chemical names of eight representative CAIs useful herein have been enumerated. In the preceding paragraph [0023], numerous patents describing compounds of this type have been identified. Thus, carbonic anhydrase inhibitors are well-known in the art.

In statement 7 on page 4 in the Official Action, it is pointed out that the application only supplies clinical data from one carbonic anhydrase inhibitor, namely dorzolamide. While the clinical data comes just from dorzolamide, we have performed pharmacologic studies in animals that show that the pharmacologic action of vasodilatation and increased oxygenation which we believe is responsible for the influence on diabetic retinas is common with several carbonic anhydrase inhibitors such as acetazolamide, metazolamide, etoxyzolamide and dorzolamide. (*Stefansson E, Pedersen DB, Jensen PK, la Cour M, Kiilgaard JF, Bang K, Eysteinsson T., Optic nerve oxygenation. Prog Retin Eye Res. 2005 May;24(3):307-32; Bach Pedersen D, Koch Jensen P, la Cour M, Kiilgaard JF, Eysteinsson T, Bang K, Wiencke AK, Stefansson E,Carbonic anhydrase inhibition increases retinal oxygen tension and dilates retinal vessels. Graefes Arch Clin Exp Ophthalmol. 2005 Feb;243(2):163-8 and Stefansson E, Jensen PK, Eysteinsson T, Bang K, Kiilgaard JF, Dollerup J, Scherfig E, la Cour M. Optic nerve oxygen tension in pigs and the effect of carbonic anhydrase inhibitors, Invest Ophthalmol Vis Sci. 1999 Oct;40(11):2756-61.)* Copies of these references are enclosed. Our studies have shown clearly that this relates to the carbonic anhydrase inhibition effect of these molecules and it is therefore reasonable to expect other carbonic anhydrase inhibitors to behave clinically in the same way as dorzolamide.

Regarding statement 8 on page 4 of the Action, it is well known (Supuran et al 2003, Stefánsson et al 2005, both cited above) that the carbonic anhydrase inhibitors share a common

fundamental structure, have the same pharmacologic action, that is, inhibition of carbonic anhydrase, influence retinal vessel diameter and oxygenation in the same way and have the same clinical effect such as lowering intraocular pressure and diureses. It is highly unlikely that they would share all these various structural and functional properties and yet behave differently than dorzolamide towards diabetic retinopathy. The principle is clear. Of course, a molecule that would be marketed for clinical use would have to be tested specifically, but its clinical effect is quite predictable from the available data.

On the bottom of page 4 and beginning of page 5 of the Action, it is stated: "Claims 6,12-26, 31 and 37-51 are indefinite as to the expression "slowing the progression of diabetic retinopathy in a diabetic not suffering from diabetes. The term, 'slowing the progression of diabetic retinopathy' indicates that the person already has had diabetic retinopathy." This statement involves a misunderstanding of the definition of diabetic retinopathy. Typically, a person who develops diabetes mellitus has no apparent ophthalmoscopical lesions in the retina for several years and during this time period the person is defined as having no retinopathy. Careful studies, such as the fluorophotometry as well as animal studies in diabetic animals demonstrate that diabetic retina in this stage has early changes which are simply not detectable by standard clinical examination such as fundus biomicroscopy and photography. The classification of no retinopathy is therefore based on the current ability for diagnosis and detection. It is a misunderstanding that this implies that nothing is going on in the retina and no development going on. Quite to the opposite, clinical studies (DCCT study group: *Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group.*

Ophthalmology. 1995 Apr;102(4):647-61.) have demonstrated that the progress towards diabetic retinopathy can be influenced quite radically by controlling blood-glucose. Most diabetics present with microaneurisms in the capillaries of the retina as the first sign of diabetic retinopathy and this usually happens 5-15 years after the onset of diabetes mellitus. At this time they are classified as having diabetic retinopathy. This is also associated with capillary occlusions in the retina. The carbonic anhydrase inhibitors dilate capillaries and we believe this is why they prevent capillary occlusions and thereby prevent the formation of microaneurisms and other signs of diabetic retinopathy. Our treatment is aimed at preventing the complication of diabetes mellitus which is diabetic retinopathy and to do so before overt signs of diabetic retinopathy are present. It is simply a matter of classification to state that a diabetic has no retinopathy before the overt signs happen and then has retinopathy. Clearly this is a gradual continuous process ultimately marked by events which are visible and detectable by clinical examination.

Claims 6, 12-26, 31 and 37-51 have been rejected under 35 U.S.C. 103(a) as purportedly being unpatentable over WO 99/446030 and Doshi et al. U. S. Patent No. 5,948,801.

The Doshi et al. patent deals with the treatment of retinal edema with brinzolamide. It is clear from the background of the invention that it is based on the premise that acetazolamide and other carbonic anhydrase inhibitors hasten the resorption of subretinal fluid, through an effect on the retinal pigment epithelium. Doshi et al. propose that brinzolamide may be useful in helping remove water from the edematous retina through its action on the retinal pigment epithelium. They specify all types of macular edema including that of diabetic retinopathy but they are

certainly not suggesting brinzolamide as a treatment for diabetic retinopathy in general. Such a claim would make no sense given the rationale and background of their invention.

And, in fact, they clearly state that retinal edema may develop in association with a variety of conditions, one of which is diabetic retinopathy (col. 1, lines 61-67); they never imply that they are treating the associated conditions, only retinal edema. In contrast, the present application is not claiming carbonic anhydrase inhibitors as treatment of macular edema. Rather, it is claiming carbonic anhydrase inhibitors as a treatment to slow down or prevent the progression towards diabetic retinopathy, which is completely different from retinal edema, even though a small minority of diabetics may develop retinal edema. Diabetic retinopathy is a potentially blinding disorder that affects the 150 million people that now have diabetes and will affect the 300 million people that will have developed diabetes within 20 years (*Zimmet P et al, Nature 414: 782-787, 2001*, copy enclosed). Less than 10% of those diabetics have macular edema (*Stefansson E, Bek T, Porta M, Larsen N, Kristinsson JK, Agardh E., Screening and prevention of diabetic blindness. Acta Ophthalmol Scand. 2000 Aug;78(4):374-85,* Klein et al. Beaver Dam Eye Study, Ophthalmology 1992; 99: 58-62 and Kristinsson JK, Diabetic retinopathy. Screening and prevention of blindness, A doctoral thesis. Acta Ophthalmol, 1997; suppl. 223; 75, p. 27-28, copy enclosed). Of the approximately 150 million diabetics in the world today, it can be estimated that 135 million do not have diabetic macular edema and approximately 75 million do not have visible diabetic retinopathy and are classified as having no retinopathy. None of these 75 million people would apply to the treatment as suggested by the patent by Doshii et al. Further, even when Doshi et al. suggest prevention of macular edema, it would presumably be on patients already having one of their associated conditions such as diabetic retinopathy. In the

present case, however, the patient is a diabetic not yet showing signs of diabetic retinopathy. Therefore, the population is different. The treatment that I propose would ideally be started when patients are diagnosed with diabetes mellitus. Patients with type I diabetes mellitus never have diabetic retinopathy when they are diagnosed and usually have no retinopathy for at least 5 years after diagnosis. Klein et al (Beaver Dam Eye Study, Ophthalmology 1992; 99: 58-62) showed that in Beaver Dam Wisconsin 10.2% of those with newly diagnosed diabetes mellitus type II had any retinopathy and thereof 2.0% had macular edema (Klein et al 1992). This indicates that at least 90% of diabetics do not have diabetic retinopathy when they are diagnosed and at least 98% do not have diabetic macular edema. It is this population that we aim to treat and make less likely that they develop towards diabetic retinopathy. We are not dealing with the very small minority (2% of newly diagnosed and as highest 10% overall) that has diabetic macular edema.

Still further, a knowledgeable person would not draw the conclusion from the invention and patent of Doshi et al that carbonic anhydrase inhibitors would be useful for diabetic retinopathy in general. The diabetic retina is not edematous in the diabetic before he develops overt signs of diabetic retinopathy and also does not have edema in most cases after that. It is only the approximately the 10% of diabetics who have diabetic macular edema where it makes sense to increase the removal of water by affecting the pigment epithelium through carbonic anhydrase inhibition. This explains why Doshi et al did not make this jump and no one has in spite of the fact that the effect of carbonic anhydrase inhibition on the subretinal fluid resorption by acetazolamide has been known for more than 20 years (*Marmor et al, Investigative of Ophthalmology 121-124, 1982*; see the background of invention by Doshi et al.) A

knowledgeable person would indeed made the distinction between diabetic macular edema (and retinal edema in general) and diabetic retina with no retinopathy as well as the diabetic retina with early non-proliferative diabetic retinopathy. The difference between the two would be obvious to a person skilled in the art. Based on the background and invention by Doshi et al, it would make absolutely no sense at all to propose that this would be useful in slowing the development towards diabetic retinopathy in a diabetic.

WO 99/44603 (Sponsel) relates to a composition and method for treating certain ocular disorders, particularly macular edema and macular degeneration, by applying a topical carbonic anyhdrase inhibitor and an ocular hypotensive agent or inotropic agent in an amount sufficient to improve visual function. Thus, Sponsel uses a combination of active agents to achieve treatment of macular disorders and improve visual function. We do neither. . As noted above, macular edema develops in association with certain conditions, including retinitis pigmentosa and diabetic retinopathy. Sponsel never suggest treatment of the underlying conditions, only of the macular edema which develops therewith. Thus, the points made with respect to Doshi et al. above are equally valid with respect to Sponsel. Most especially, it is again pointed out that even if Sponsel is taken as suggesting use of his agents to prevent macular edema, the patients would already have manifested the associated conditions, e.g., diabetic retinopathy. However, in the present invention, the patient is diabetic but has not yet manifested signs of diabetic retinopathy. Therefore, the population is different.

We are proposing a treatment for patients with diabetes mellitus that do not yet have diabetic retinopathy.

Sponsel et al are proposing a treatment for retinal edema. They point out that a number of diseases may cause retinal (macular) edema, including retinitis pigmentosa, branch retinal vein occlusion and diabetic retinopathy. They do not suggest and knowledgeable person would not reason that they are proposing treatment for retinitis pigmentosa or diabetes mellitus. Their patent is 5 years old and neither Sponsel et al nor anybody else has suggested that their patent extends beyond the treatment of retinal edema.

Our target population is newly diagnosed diabetics. They usually do not have retinopathy. Type I diabetics never have retinopathy at diagnosis. Type 2 diabetics may be diagnosed late and therefore a few of them have retinopathy. Klein et al found that 10% of newly diagnosed type II diabetics have retinopathy (90% do not) and 2% have macular edema (98% do not) (Klein et al. Beaver Dam Eye Study, Ophthalmology 1992; 99: 58-62).

In most epidemiologic studies the majority of diabetics do not have retinopathy. A small minority of diabetics have macular (retinal) edema, in most studies 1-10% of diabetics (Klein et al. Beaver Dam Eye Study, Ophthalmology 1992; 99: 58-62 and Kristinsson JK, Diabetic retinopathy. Screening and prevention of blindness, A doctoral thesis. Acta Ophthalmol, 1997; suppl. 223; 75, p. 27-28). Diabetic eye disease has several stages. In the beginning of the disease no type I diabetics and very few (10%) type II diabetics have retinopathy, and the overwhelming majority has no retinopathy. With increasing duration of diabetes mellitus the majority of diabetics develop non-proliferative (background retinopathy). A proportion of those then go on to develop diabetic macular edema. This can be seen as 3 stages where stage 1 is no retinopathy, stage 2 is non-proliferative retinopathy and stage 3 is diabetic macular edema. The treatment suggested by Sponsel et al and Dorsi et al is directed specifically at the complication of retinal

edema that occurs in a number of eye diseases, and may also happen in diabetics and only in those who already have diabetic retinopathy which is identifiable by ophthalmoscopy. In no cases do diabetics develop directly from no retinopathy to macular edema. The patents by Dorsi et al and Sponsel et al do not give a rationale and do not suggest to the knowledgeable person that their treatment would be useful for diabetic retinopathy in general, any more than it would be useful for retinitis pigmentosa in general. It would be stretching the point even further to suggest that they are proposing drug treatment that should be used for diabetics who do not have retinopathy. No knowledgeable person would make that connection based on the patent and the background by Dorsi et al and Sponsel et al. Indeed the entire field of knowledgeable person including Drs' Dorsi and Sponsel have had the opportunity to do so over at least 5 years and have not done so and this strongly supports my claim that this connection cannot be made based on the data and thesis set forth in their patents.

Further, present Claim 31 and dependent Claims 37-51 require that the carbonic anhydrase inhibitor be the sole agent administered to slow the progression of diabetic retinopathy, while Sponsel's method requires a combination of a carbonic anhydrase inhibitor and another active agent for his treatment.

14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: May 17, 2005

Einar Stefansson

EINAR STEFANSSON, M.D., PH.D.